Beyond Analogy: Autoimmune Origins of Psychiatric Disorder

The immune system's failure of self/non-self discrimination as a direct mechanism of mental illness

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ABSTRACT

The analogy between autoimmune disease and psychosis — both failures of the self/non-self distinction — has been noted in the philosophical literature. This article argues that the relationship is more than structural: in a significant and systematically underestimated subset of cases, what clinical psychiatry diagnoses as primary mental disorder is an autoimmune disease of the brain, either unrecognized or subclinical. Drawing on recent large-scale epidemiological evidence, mechanistic immunology, and clinical observations across lupus, Hashimoto's thyroiditis, and anti-NMDA receptor encephalitis, the article traces four converging lines of evidence: epidemiological co-occurrence, shared genetic architecture, direct mechanistic pathways from autoantibodies to psychiatric symptoms, and therapeutic response to immunomodulation. Particular attention is paid to the subclinical problem: the long diagnostic lag during which autoimmune activity drives psychiatric presentations that are treated as primary psychiatric illness. The philosophical framework of Preschel (2026) — that complexity is a relational property, a measure of the distance between what is there and what our cognitive apparatus can represent — is applied to argue that psychiatric nosology has mistaken features of its descriptive models for features of the disorders themselves. The brain and the immune system are not merely analogous in their failure modes; they interact, and that interaction is being systematically missed.

KEYWORDS: autoimmune encephalitis · psychoneuroimmunology · subclinical Hashimoto's · NMDA receptor antibodies · neuroinflammation · psychiatric misdiagnosis · philosophy of nosology · limbic neuroinflammation · complexity · self/non-self discrimination

1. Introduction: The Analogy That Is a Mechanism

In a recent essay on the concept of complexity in science, Preschel (2026) observes that the immune system makes catastrophic errors of self-recognition that produce autoimmune disease — errors he describes as *'structurally analogous to the brain's psychoses.'*[1] The observation is precise and philosophically productive: both the immune system and the psychotic mind fail at the same fundamental task — discriminating between self and non-self, between what belongs to the organism and what threatens it.

The analogy, however, may be considerably less analogical than it appears. The present article argues that in a significant subset of clinical cases, the relationship between these two failure modes is not structural resemblance but direct causation. The immune system's failure of self-recognition generates autoantibodies that cross the blood-brain barrier, bind to neural

receptors, and produce, through a chain of mechanistic steps now increasingly well characterized, precisely the psychiatric symptoms that clinical nosology classifies as primary mental illness.

This argument has consequences both clinical and philosophical. Clinically, it implies that a proportion of patients currently cycling through psychiatric treatment — receiving psychotropic medications aimed at a symptomatic superstructure — have an underlying autoimmune substrate that is not being addressed, and in some cases not even sought. Philosophically, it implies something Preschel's own framework licenses: that psychiatric diagnostic categories, like all models, are representations of the world rather than features of it, and that in this domain our models have been mistaken in a particularly consequential way.

> *"Simplicity exists in our models. It exists in our descriptions. It exists in the convenient fictions that make mathematics tractable and communication possible. But it does not exist in the world those models are trying to describe."*
>
> PRESCHEL, NOTHING IS SIMPLE (2026)

What is true of simplicity is equally true of the diagnostic categories of psychiatry. Depression, anxiety, delusional disorder, schizophrenia — these are models, not natural kinds. They are useful at a certain resolution. But the evidence reviewed here suggests that below the resolution at which these categories operate, there is a mechanistic reality — immunological, biochemical, anatomical — that they do not capture, and that they have actively obscured by providing labels that stop inquiry rather than advance it.

2. The Epidemiological Signal

The association between autoimmune disease and psychiatric disorder is now established at population scale. A 2025 study published in *BMJ Mental Health*, analyzing data from 1,563,155 adults in the UK's 'Our Future Health' cohort — the world's largest consented cohort study — found that individuals with autoimmune conditions faced approximately double the risk of affective disorders compared to the general population, across diagnoses of depression, bipolar disorder, and anxiety.[2]

This association is not explained by shared environmental exposure or psychological response to chronic illness, though both contribute. The genetic architecture of the relationship is equally compelling. A 2025 study in *Translational Psychiatry*, using Genomic Structural Equation Modeling across eleven immune-mediated diseases and thirteen psychiatric disorders, confirmed consistent genetic correlations across the autoimmune-psychiatric interface.[3] Genome-wide association studies of autoimmune rheumatic and endocrine diseases have revealed shared genetic haplotypes with psychiatric disorders including schizophrenia and depression, operating through the HLA complex and related immune-regulatory loci.[4]

Most strikingly for schizophrenia specifically, the largest GWAS studies have found that the genetic loci associated with the condition are strongly enriched in B-lymphocyte lineages involved in acquired immunity — the CD19 and CD20 cell lines.[5] This is not the genetic signature of a purely neurological condition. It is, in part, the genetic signature of an immune condition.

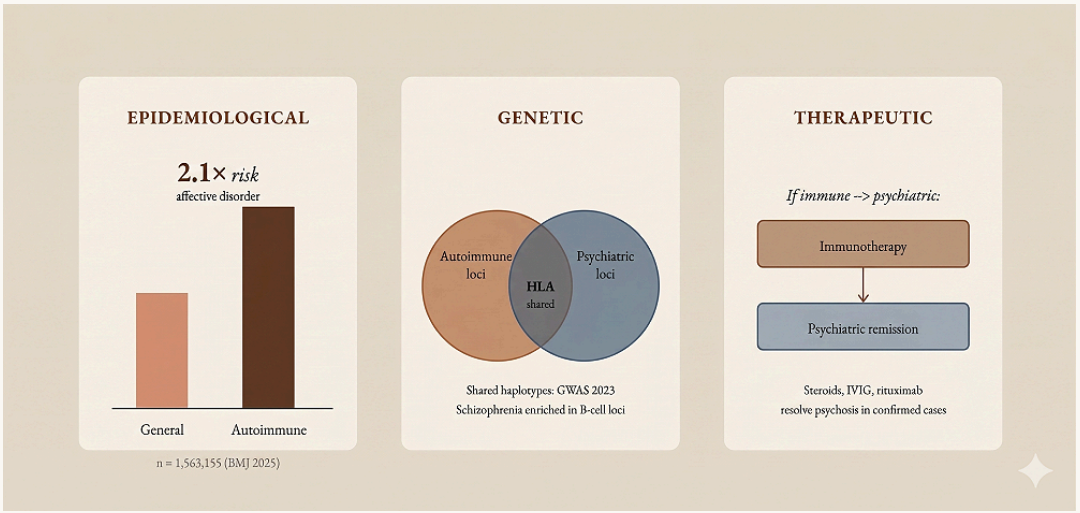

Figure 1. Three convergent lines of epidemiological and genetic evidence. Left: autoimmune conditions double the risk of affective disorder (BMJ Mental Health, 2025; n = 1,563,155). Centre: shared genetic haplotypes — particularly in the HLA complex — link autoimmune rheumatic diseases with schizophrenia and depression. Right: immunotherapy produces psychiatric remission in confirmed autoimmune cases, satisfying the causal criterion.

3. The Mechanism: Autoantibodies, Receptors, and the Blood-Brain Barrier

The clearest proof of principle comes from anti-NMDA receptor encephalitis, first fully characterized in 2007. The condition is caused by immunoglobulin G antibodies targeting the GluN1 subunit of the N-methyl-D-aspartate receptor. These antibodies — produced by the peripheral immune system in a canonical autoimmune error — cross the blood-brain barrier when it is disrupted and bind to NMDA receptors on neuronal membranes, causing receptor internalization and functional hypofunction.[6]

The significance of this mechanism extends well beyond the specific syndrome. Since the early 1990s, NMDA receptor hypofunction has been the leading mechanistic hypothesis for schizophrenic psychosis — supported by the observation that NMDA antagonists such as phencyclidine and ketamine reliably produce schizophrenia-like symptoms in healthy subjects. Anti-NMDA receptor encephalitis demonstrates that this hypofunction can be produced directly by an autoimmune mechanism, without any genetic predisposition to schizophrenia in the classical sense. Patients with the condition develop hallucinations, paranoid delusions, catatonia, and disorganized behavior that are clinically indistinguishable from acute schizophrenia. When the antibody load is reduced by immunotherapy, the psychiatric symptoms resolve.[7]

This is not an analogy. It is a mechanism.

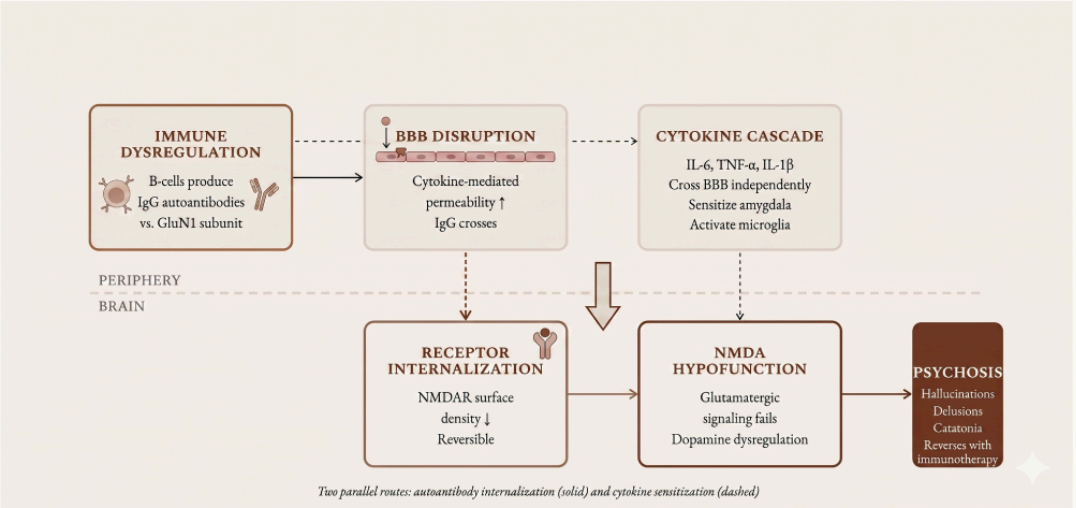

Figure 2. The autoimmune-to-psychiatric pathway in anti-NMDA receptor encephalitis. Peripheral B-cells produce IgG autoantibodies targeting the GluN1 subunit. Via two parallel routes — direct antibody crossing of a disrupted blood-brain barrier and cytokine-mediated neuroinflammation — these antibodies internalize NMDA receptors, produce functional hypofunction, and generate psychiatric symptoms clinically indistinguishable from primary schizophrenia. The process is reversible: reduction of antibody load by immunotherapy produces psychiatric remission, confirming the causal direction.

The cytokine pathway operates in parallel and independently of the antibody mechanism. Pro-inflammatory cytokines — IL-6, TNF-α, IL-1β — produced during autoimmune activity cross the blood-brain barrier through their own mechanisms, directly sensitize amygdalar circuits involved in threat appraisal, reduce serotonergic tone in limbic structures, and activate microglial populations that produce further neuroinflammatory cascades.[8] This pathway is relevant across all autoimmune conditions, not only those producing specific antineuronal antibodies.

4. The Subclinical Problem

4.1 THE ICEBERG AND ITS VISIBLE FRACTION

The most clinically important dimension of this argument concerns not the dramatic, detectable cases — autoimmune encephalitis presenting with acute psychosis and seizures — but the subclinical cases: patients in whom autoimmune activity is present, measurable, and neuropsychiatrically active, but in whom the clinical threshold for an autoimmune diagnosis has not been reached. These patients present to psychiatry. They receive psychiatric diagnoses. They are treated with psychotropic medications aimed at their symptoms. The autoimmune substrate is not investigated, and in many cases not even considered.

Hashimoto's thyroiditis provides the paradigm case. Standard clinical practice treats the condition as a thyroid disease and waits until thyroid function — measured by TSH — exceeds the normal range before initiating treatment. But the autoimmune process begins long before

this threshold is crossed. Elevated anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TgAb) antibodies indicate active immune attack on the thyroid gland from the moment of their elevation. And the psychiatric consequences of this attack are not mediated solely by thyroid hormone levels.

A pivotal study found that patients with Hashimoto's thyroiditis who were euthyroid — thyroid function technically normal — nonetheless showed significantly elevated rates of major depression and anxiety disorders compared to controls, and that this excess could not be explained by hormonal deficit alone, implicating the autoimmune process itself as the psychiatric driver.[9] The mechanism proposed is direct: TPO antibodies have been detected in cerebrospinal fluid; they cross-react with antigens expressed in brain tissue; they trigger microglial activation preferentially in limbic-rich structures including the amygdala and hippocampus — precisely the circuits governing emotional appraisal, affective memory, and the regulation of close relational bonds.

> *Rare severe cases of Hashimoto's encephalopathy presenting with mood disorder may represent only the tip of an iceberg.*
>
> — Vonk et al., Biological Psychiatry (2007)

This iceberg metaphor is apt. The clinical literature recognizes Hashimoto's encephalopathy — the overt, steroid-responsive, seizure-associated syndrome — as a known neuropsychiatric entity. What it has not systematically recognized is the vast subclinical mass below the diagnostic waterline: patients in whom the autoimmune process is active and neuropsychiatrically consequential, but who have never met criteria for encephalopathy, and who have never been offered immunological investigation of their psychiatric symptoms.

4.2 LUPUS AND THE PRODROME

Systemic lupus erythematosus offers a particularly clear demonstration of the diagnostic lag. A 2024 mixed-methods study in *eClinicalMedicine* (the INSPIRE project) found that psychiatric symptoms — including mood disorders, perceptual disturbances, and what patients described as a 'feeling of unreality' — frequently preceded the formal diagnosis of lupus by months to years.[10] These were not secondary responses to chronic illness; they were prodromal manifestations of an as-yet-undiagnosed autoimmune condition.

One documented case involved a patient diagnosed with borderline personality disorder six months before their lupus diagnosis, who observed that the symptoms of one 'got under control' when the symptoms of the other did — a natural experiment in the causal relationship between the two conditions. Clinicians in the INSPIRE study noted that young women presenting with new-onset psychosis were sometimes admitted to psychiatric wards and treated with antipsychotics, when what they needed was 'a lot of steroids.'[10]

A further methodological problem compounds the issue: protocols that exclude neuropsychiatric symptoms predating the lupus diagnosis by more than two years as 'unrelated' assume that the diagnostic date reflects the disease onset. Given that SLE has a typical diagnostic delay of several years, this assumption systematically misclassifies prodromal autoimmune psychiatric symptoms as primary psychiatric illness.[10]

5. The Misdiagnosis Pipeline and Its Consequences

The convergence of clinical presentations produces a systematic misdiagnosis pipeline. Autoimmune diseases share symptomatic overlap with psychiatric conditions — anxiety, depression, perceptual disturbances, fatigue, sleep disruption — that is not incidental but mechanistic, arising from shared neuroinflammatory pathways. Autoimmune conditions frequently flare and remit, producing variable presentations depending on when the patient is assessed. And autoimmune diseases are significantly more common in women, a population whose somatic symptoms have historically been more readily attributed to psychological causes in medical settings.[11]

A 2025 mixed-methods study of over 3,000 participants with systemic autoimmune rheumatic diseases found that patients whose autoimmune disease had been misdiagnosed as psychosomatic or psychiatric showed persistently elevated rates of depression, anxiety, and impaired mental wellbeing, as well as damaged trust in healthcare services — effects that persisted for decades after the misdiagnosis.[12] More than 80% reported damage to their sense of self-worth. This is not merely a diagnostic failure. It is a harm.

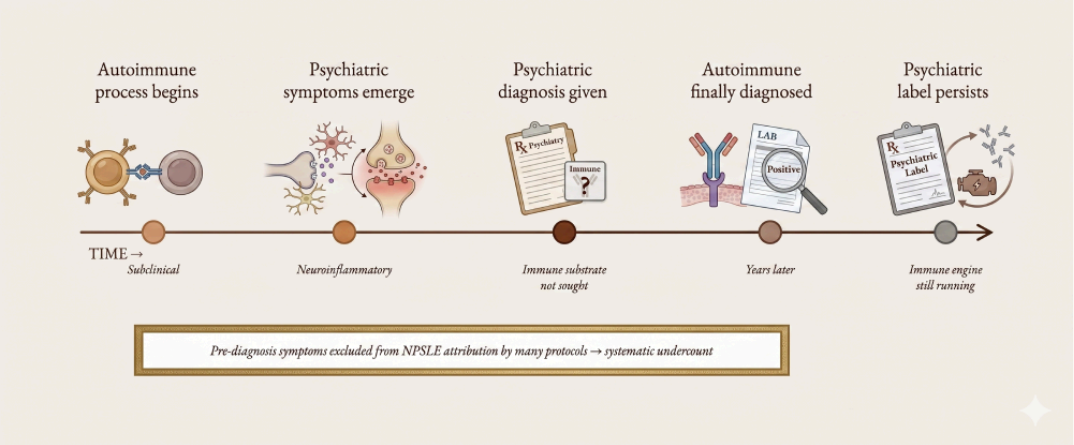

Figure 3. The misdiagnosis timeline. Autoimmune disease begins subclinically, drives psychiatric symptoms through neuroinflammatory mechanisms, receives a psychiatric diagnosis — and the autoimmune substrate is not investigated. When the autoimmune disease is eventually diagnosed, the psychiatric label often persists, and protocols that exclude pre-diagnosis neuropsychiatric symptoms as 'unrelated' systematically undercount the true prevalence of autoimmune psychiatric manifestations.

A clinical recommendation emerging from this literature is direct and actionable: patients with newly detected psychiatric disorders that respond poorly to standard pharmacological management should be investigated for underlying systemic autoimmune disease before the treatment-resistant label is applied.[13] Treatment resistance — the patient who does not respond to antidepressants, mood stabilizers, or antipsychotics — may be less a property of the psychiatric disorder than a signal that the disorder has been misclassified.

6. The Philosophical Dimension: Models Mistaken for Reality

Preschel (2026) argues, following Wittgenstein, that scientists using the word 'complexity' are making a hidden ontological commitment: that simplicity exists as the baseline against which complexity is measured, when in fact simplicity is always a property of our models rather than of the things they describe.[1] The argument generalizes directly to psychiatric nosology.

Psychiatric diagnostic categories — depression, schizophrenia, bipolar disorder, personality disorder — are models. They are useful at a certain resolution: they organize clinical observations, guide treatment decisions, facilitate communication between clinicians and patients, and support epidemiological research. But they are not natural kinds in the sense of carving nature at its joints. They are, in Preschel's terms, simplified representations that make clinical practice tractable, at the cost of obscuring the depth of what is actually there.

What is actually there, in the cases reviewed here, is a continuous mechanistic process running from peripheral immune dysregulation through cytokine-mediated neuroinflammation, blood-brain barrier disruption, autoantibody binding to neural receptors, disruption of glutamatergic and dopaminergic signalling, microglial activation, hippocampal remodeling, and amygdalar sensitization — producing, at the level of experience and behavior, what we label depression, anxiety, paranoia, or psychosis. The psychiatric label sits at the end of this causal chain. It names the output, not the mechanism. And naming only the output, without investigating the mechanism, produces treatments aimed at the output that leave the mechanism running.

> *When scientists use 'complexity,' they are variously measuring, confessing ignorance, marking prestige boundaries, and performing humility before audiences. What they are never quite doing is accurately describing an intrinsic property of the world — because intrinsic properties of this kind, independent of any observer and any model, are precisely what physics, biology, and philosophy have spent a century teaching us to be deeply suspicious of.*
>
> — Preschel, Nothing Is Simple (2026)[1]

The same critique applies to psychiatric diagnosis. Schizophrenia, as a label, does not describe an intrinsic property of the person so labeled. It describes the output of a clinical assessment at a particular moment, using instruments shaped by cultural and institutional history, applied to a phenomenon that has multiple etiologies — some genetic, some developmental, some immunological — which the label does not distinguish. The label is a model. In the autoimmune subset, it is a model that has been mistaken for the thing, with the consequence that the thing — the immune mechanism — goes untreated.

Preschel (2026) cites Orgel's Second Rule, as adopted by Dennett: evolution is cleverer than you are.[1] If the products of evolution are likely to be more complex than our models of them, this applies with particular force to the immune system — which did not evolve to be legible to immunologists — and to its interactions with the brain. The autoimmune-psychiatric interface is a domain where the system is consistently more than our best model of it.

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7. Therapeutic Implications and Immunotherapy Evidence

The strongest causal evidence comes from treatment. If psychiatric symptoms have an autoimmune substrate, immunotherapy should produce psychiatric remission. This prediction is confirmed, with growing consistency, in the literature.

In confirmed autoimmune encephalitis — including anti-NMDA receptor, anti-LGI1, and anti-CASPR2 subtypes — first-line immunotherapy with corticosteroids, intravenous immunoglobulins, or plasmapheresis produces psychiatric remission in a substantial proportion of patients. Those failing first-line therapy receive rituximab or cyclophosphamide, with further response rates documented.[14] In the largest outcome study, 81% of anti-NMDA receptor encephalitis patients had substantial recovery at 24 months — a recovery rate that would be extraordinary for primary schizophrenia treated by any means currently available.

Beyond established autoimmune encephalitis, rituximab — which depletes B-lymphocytes and is used in rheumatoid arthritis, multiple sclerosis, and anti-NMDA receptor encephalitis — has been investigated as add-on therapy in treatment-resistant schizophrenia and obsessive-compulsive disorder. A pilot study found clinically meaningful improvement in a subset of markedly ill, treatment-resistant patients, with cytokine changes and altered functional connectivity as putative mediating mechanisms.[15]

8. Conclusion

Preschel (2026) observes that the immune system is at least as complex as the human brain by certain measures, and that the comparison between them reflects the observer's choice of metric rather than any intrinsic difference in their complexity.[1] The present article has argued something that extends this observation: the brain and the immune system do not merely exist in parallel as rival candidates for maximum complexity. They interact. In a subset of cases that is larger than current clinical practice recognizes, the immune system's complexity — its adaptive responses, its antibody-generating machinery, its cytokine cascades — reaches directly into the brain and shapes the experiences and behaviors that psychiatry then labels, treats, and too often misunderstands.

The analogy Preschel identifies between autoimmune self-attack and psychotic self-misrepresentation is real, structurally illuminating, and philosophically precise. But the relationship is not merely analogical. The membrane that the immune system mistakes for foreign tissue and the brain circuits that produce disordered cognition are connected — through antibodies, cytokines, the blood-brain barrier, and the limbic structures that regulate both emotional life and the appraisal of threat. In the subset of cases where this connection is causal, treating only the psychiatric output while leaving the immunological engine running is not a neutral clinical decision. It is an error — one whose causes include the very conceptual structures that psychiatric nosology has, in Preschel's terms, mistaken for properties of the world rather than features of our models.

The corrective requires not the abandonment of psychiatric categories but their supplementation with immunological investigation — particularly in treatment-resistant presentations, in conditions with known autoimmune associations, and in cases where the phenomenology does not fit cleanly within existing diagnostic frameworks. The distance between what is there and what our current models can represent turns out, in this domain, to be consequential for patients.

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AUTHOR DECLARATION

Richard Preschel declares no conflicts of interest. This article was prepared as an independent scholarly work. The philosophical framework draws extensively on the author's prior publication: Preschel, R. (2026), Nothing Is Simple: On a Word Scientists Forgot to Question. All quotations from that work are self-citations by the author.